Severe antenatally diagnosed renal disorders: background, prognosis and practical approach

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Abstract

Nowadays most renal disorders, especially urinary tract malformations and renal cystic disease, are diagnosed antenatally. In cases of severe bilateral disease, intrauterine renal dysfunction may lead to renal oligohydramnios (ROH), resulting in pulmonary hypoplasia which affects perinatal mortality and morbidity as well as the long-term outcome. However, some infants may only have mild pulmonary and renal disease, and advances in postnatal and dialysis treatment have resulted in improved short- and long-term outcome even in those infants with severe ROH. Here, we review the current state of knowledge and clinical experience of patients presenting antenatally with severe bilateral renal disorders and ROH. By addressing underlying mechanisms, intrauterine tools of diagnosis and treatment as well as published outcome data, we hope to improve antenatal counselling and postnatal care.

Key summary points

1. Nowadays most renal disorders are diagnosed antenatally, especially urinary tract malformations and renal cystic disease.
2. Severe kidney dysfunction may lead to renal oligohydramnios, which can cause pulmonary hypoplasia and is a risk factor of perinatal mortality and postnatal renal outcome. However, as considerable clinical heterogeneity is present, outcome predictions need to be treated with caution.
3. Advances in postnatal and dialysis treatment have resulted in improved short- and long-term outcomes even in infants with severe renal oligohydramnios.
4. A multidisciplinary approach with specialist input is required when counselling a family with an ROH-affected fetus as the decision-making process is very challenging.

Keywords Antenatal · Ultrasound · Renal oligohydramnios · Outcome · Chronic kidney disease · Congenital anomalies of kidney and urinary tract · Pulmonary hypoplasia

Introduction

The diagnosis of renal disease in the fetus is nowadays often established by ultrasound examination prior to birth. Fortunately, most disorders are unilateral and usually carry a good prognosis. In contrast, bilateral renal disorders often lead to antenatal renal dysfunction that are characterized by decreased fetal urine output and result in renal oligohydramnios (ROH). In such cases, short- and long-term prognosis is more pessimistic, especially as lung development may also be affected (pulmonary hypoplasia) [1–3].

The extreme form of ROH, bilateral renal agenesis (Potter's syndrome), has been regarded as incompatible with life. However, other underlying renal disorders causing ROH, such as lower urinary tract obstruction (LUTO) or autosomal-recessive polycystic kidney disease (ARPKD), are not automatically associated with a fatal prognosis. Unfortunately, the term Potter "sequence" is still occasionally used in this setting, irrespective of the underlying renal diagnosis [4, 5]. In our opinion and the opinion of many experts in the field, the term should be abandoned and replaced by specific diagnoses to avoid confusion.

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The aim of this review is to address advances in the diagnostic approach, treatment options and clinical outcome (short- and long-term) of children born with ROH in order to improve the antenatal and postnatal clinical care and counselling of affected patients and families.

Definition of ROH

The amount of amniotic fluid (AF) can be directly measured at the time of a cesarean section or by dye dilution techniques, with both approaches being very accurate in terms of identifying abnormally high or low levels of AF. Because these methods are invasive and time-consuming, ultrasound-based methods have been introduced to estimate the AF volume (AFV), such as the amniotic fluid index (AFI) [6] and single deepest pocket (SDP) [7, 8]. The AFI, also called the four-quadrant assessment, is defined as the sum of the largest vertical fluid pocket in each of the four quadrants of the maternal abdomen. An AFI threshold of <5 is generally accepted as a definition of oligohydramnios [9]. The SDP is defined as the fluid pocket with the largest diameter measured vertically and transversally at any location in the amniotic cavity [7, 8]. There is still some variation in its definition. For instance, the definition of normal AFV was altered from a >1 -cm pocket in one plane to a 1-cm pocket in two perpendicular planes, and ultimately to a 2-cm vertical pocket with a 1-cm horizontal measurement [10]. The latter definition has gained wide acceptance in the literature [11], although there still is no final consensus on the definition of ROH.

Fetal kidneys contribute to AFV around gestational week 14. Since the development of ROH may be a dynamic process, the time of first diagnosis of ROH may have an important clinical impact, a problem that has not been addressed systematically. Whether ROH diagnosed at a gestational age <20 weeks is associated with further complications [justifying termination of the pregnancy (TOP)] has not been studied prospectively. Based on the observations in our own centre there are individual patients with benign outcome despite the early detection of ROH. Nevertheless, technical limitations or individual reasons (poorly supervised pregnancies) often do not allow an early diagnosis in practice.

Other, yet unknown, factors might also contribute to AFV estimation. One study correlating AFI and amnioinfusion volume found that 35 % of the AFI measurements were accounted for by factors other than AFV [12]. Also, a substantial intra-observer variation, such as due to inadequate equipment and training, has to be taken into account. Most importantly, however, is the fact that the correlation of estimated AFV with the actual fluid volume remains unsatisfactory due to a missing definition of abnormal AFV at any point in gestation [9]. Therefore, it seems problematic to base clinical guidelines solely on the estimated AFV. Hence, referral of

fetuses with suspected abnormal findings to specialized and experienced investigators is mandatory.

Antenatal imaging of the fetal urogenital tract and lungs

Non-invasive visualization of the fetus by ultrasound is one of the greatest advances in obstetrical medicine. From the first picture of a fetal head in 1958 by Ian Donald to the technique of fetal 3D images in the mid 1990s there has been a breakthrough in the antenatal detection of pathologies [13]. Subsequently, the assessment of fetal anatomy, especially of the heart and urogenital tract, has become standard procedure. The sensitivity of ultrasound in diagnosing fetal renal abnormalities in the second trimester of pregnancy is high [14]. In a retrospective analysis of a cohort of almost 30,000 cases, Melo et al. found that 76 % of patients with congenital kidney malformation were diagnosed by antenatal ultrasound [15]. In a retrospective study from the UK, the prenatal diagnosis of urinary tract anomalies by ultrasound corresponded with the postnatal diagnosis in 88.8 % of cases [16].

While diagnosing abnormal renal anatomy is relatively easy, the prediction of postnatal renal function and outcome is much more challenging. In one study of fetal hyperechogenic kidneys (mostly due to ARPKD), the presence of ROH and a kidney size of >4 standard deviations (SD) had a negative impact on outcome [17]. Morris et al. [18] performed a systematic review that included 215 pregnancies with ultrasound evidence of congenital LUTO in which they evaluated the accuracy of fetal ultrasound to predict postnatal renal function. Any described ultrasound parameter was considered in the analysis (i.e. amount of AF, appearance of renal cortex, renal pelvis diameter). In the meta-analysis of subgroups, abnormal renal cortical appearance (defined as the appearance of renal cortical cysts or raised renal parenchyma echogeneity) and oligohydramnios provided some accuracy in predicting poor postnatal renal function. A serum creatinine concentration of >1.2 mg/dl corresponded with the nadir of kidney function. Additionally, renal cortical appearance demonstrated a high predictive accuracy for renal dysplasia on autopsy or biopsy. More precisely, an abnormal renal cortical appearance on the ultrasound image had the best predictive value for postnatal kidney function with a sensitivity of 0.57 and a specificity of 0.84. The presence of oligohydramnios resulted in a sensitivity of 0.63 and a specificity of 0.76. Nevertheless, the authors concluded that the quality of evidence is still limited, and there is significant heterogeneity in the reported results.

To overcome the diagnostic limitations of ultrasonography, complimentary magnetic resonance imaging (MRI)

techniques have been used to evaluate renal anatomy and function. In a series of 24 fetuses with either oligohydramnios or suspected urinary tract abnormality, Poutamo et al. [19] obtained additional information in eight of 24 cases by MRI compared to ultrasound alone. Especially in the setting of oligohydramnios due to kidney agenesis or renal hypoplasia, ultrasound results were partially equivocal, while better results were obtained (in combination) with MRI imaging than with ultrasound alone [19]. Gupta et al. conducted a prospective study in which they performed MRI studies of fetuses with suspected renal abnormalities based on sonographic examination. These authors reported that MRI results confirmed ultrasound findings in 70.4 % of fetuses and supplied additional information in 25.9 % [20]. Especially in fetuses with ROH, MRI may therefore provide more specific information that can be important for postnatal management and prognosis.

The evaluation of antenatal lung development is problematic, and both ultrasound and MRI techniques have been applied in such evaluations. To date, no systematic prospective studies have been performed. Different biometric indices based on ultrasound techniques enable the examiner to estimate the degree of lung hypoplasia, such as lung volumetry, perinatal flow and Doppler velocimetry. Whether these techniques can be predictive for pulmonary hypoplasia or useful to differentiate between lethal- and non-lethal pulmonary hypoplasia needs further evaluation [21].

In ROH, the visualization of the fetal lungs by ultrasound can be poor, and MRI techniques have thus been applied since healthy fetal lungs are easy to visualize on MR images because they are filled with amniotic fluid and not with air. Nevertheless, due to the missing definition of fetal lung volumes at different points of gestation [22] and only small patient numbers, no statement can currently be made on the value of MRI techniques to predict postnatal pulmonary function in patients with ROH.

Antenatal biochemical evaluation of fetal renal function

Renal oligohydramnios is only a gross marker of fetal renal dysfunction. Fetal biochemical markers have been studied with the aim of being able to predict the degree of (postnatal) renal dysfunction and outcome (Tables 1 and 2). The measurement of electrolytes and other metabolites, such as β 2-microglobulin (β 2-MG) and cystatin C (CyC), can be undertaken either in fetal urine (by urine sampling from fetal renal pelvis, ureter or bladder) or in fetal blood (by fetal blood sampling from the umbilical vein). Both procedures carry the risk for complications, such as premature rupture of membranes, uterine contractions and preterm birth or fetal death.

The first data from fetal urine examinations were collected in 1985 by Glick et al. [23] who studied the urine of 20 fetuses

with congenital hydronephrosis and compared the findings with the postnatal outcome. An increased concentration of urinary sodium (>100 mEq/ml), chloride (>90 mEq/ml) and high urine osmolality (>210 mOsm) predicted a poor outcome after birth [23]. These findings could not be confirmed in a subsequent study of five cases of bilateral hydronephrosis in which a high variability of urine electrolytes was documented [24]. Other studies (several from the same centre) assessing fetal urine parameters and their impact on outcome are presented in Table 1. It should be noted that urine sampling might be difficult—if not impossible—especially in fetuses with no or minimal urine production. Furthermore, urine electrolyte imbalances may be due to tubular dysfunction and can be normal in glomerular anomalies. All in all, the ability of urinary electrolytes to predict long-term postnatal renal function remains controversial due to the lack of sensitivity, although in some centres it is still widely practised.

β 2-MG and CyC do not cross the placenta and hence are not removed by the mother's metabolism. They can therefore be obtained by sampling fetal urine or blood and used to predict kidney function in utero. Muller et al. [25] conducted a prospective cohort study on 42 children with isolated obstructive uropathy and analysed the concentration not only of urinary sodium, but also of urinary β 2-MG. They found that β 2-MG was the superior marker in terms of both sensitivity (0.8) and specificity (0.83) in predicting postnatal renal function [25]. The same team also found a good correlation between fetal urinary CyC and postnatal serum creatinine at 1 year of age [26]. In a systematic review by Morris et al. [27], the problem of the accuracy of urine electrolyte testing, including β 2-MG, in predicting renal outcome after birth was addressed. These authors concluded that, due to small study samples and varying thresholds of urinary markers, fetal urine analysis is still not helpful in predicting postnatal renal outcome [27]. Novel laboratory techniques, such as proteomics, may overcome some of these problems, but so far data are not available.

More recently, studies have assessed the concentrations of β 2-MG and CyC in fetal serum (Table 2). The advantage of serum measurements over urinary ones is the reflection of glomerular function. The chosen cut-off of β 2-MG in most studies was 5 mg/l. In contrast to CyC, β 2-MG decreased significantly with gestational age and had a higher specificity for the prediction of impaired renal function although the diagnostic efficiency was equal. Fetuses with impaired renal function at birth or who were aborted for renal malformations had higher CyC concentrations, while the β 2-MG concentration was increased only in fetuses who were aborted. However, values of β 2-MG of <5 mg/l do not necessarily predict a good renal outcome. For example, in lower urinary tract obstruction, glomerular filtration may be normal when the umbilical vein puncture takes place before progressive renal damage occurs. Consequently, although these studies indicate that

Table 1 Fetal urine biochemical markers

Fetal marker	Reference	Number of patients	Assumed prognosis	Predictive value	Limitations
Sodium (Na^{2+}) (urine)	Glick et al. (1985) [23]	20	$\text{Na}^{2+} > 100$ mEq/ml: poor $\text{Na}^{2+} < 100$ mEq/ml: good	In 90 %, correct prediction of prognosis	Invasive procedure
	Elder et al. (1990) [24]	5	$\text{Na}^{2+} > 100$ mEq/ml: poor $\text{Na}^{2+} < 100$ mEq/ml: good	Not predictive	
	Muller et al. (1993) [25]	100	$\text{Na}^{2+} > 50$ mmol/l: poor	Specificity 64 % Sensitivity 82 %	Insufficient to predict postnatal renal function
	Muller et al. (1999) [26]	71	$\text{Na}^{2+} > 75$ mmol/l: poor	Specificity 98 % Sensitivity 100 %	
	Anumba et al. (2005) [59]	113	$\text{Na}^{2+} > 50$ mmol/l: poor	Sensitivity 33 %	Fetal risks
	Migueluez et al. (2006) [60]	39	$\text{Na}^{2+} > 2$ SD	Specificity 100 % Sensitivity 44 %	
				Slightly improved prediction of renal function	
	Craparo et al. (2007) [61]	12	$\text{Na}^{2+} > 100$ mEq/l: abnormal	Not predictive for potential response to shunting	
Chloride (Cl^-) (urine)	Glick et al. (1985) [23]	20	$\text{Cl}^- > 90$ mEq/ml: poor $\text{Cl}^- < 90$ mEq/ml: good	In 90 % correct prediction of prognosis	Invasive procedure
	Elder et al. (1990) [24]	5	$\text{Cl}^- > 90$ mEq/ml: poor $\text{Cl}^- < 90$ mEq/ml: good	Not predictive	
	Muller et al. (1993) [25]	100	$\text{Cl}^- > 50$ mmol/l: poor	Specificity 62 % Sensitivity 70 %	Fetal risks
	Migueluez et al. (2006) [60]	39	$\text{Cl}^- > 2$ SD	Specificity 70 % Sensitivity 56 %	
				Slightly improved prediction of renal function	
Potassium (K^+) (urine)	Glick et al. (1985) [23]	20		Not predictive	Invasive procedure
Osmolarity (urine)	Glick et al. (1985) [23]	20	Osmolarity > 210 mOsm: poor Osmolarity < 210 mOsm: good	In 90 % correct prediction of prognosis	
	Elder et al. (1990) [24]	5	Osmolarity > 210 mOsm: poor Osmolarity < 210 mOsm: good	Not predictive	
Creatinine (urine)	Glick et al. (1985) [23]	20		Not predictive	Invasive procedure
	Muller et al. (1993) [25]	100	Creatinine < 200 $\mu\text{mol/l}$: poor	Specificity 54 % Sensitivity 64 %	
Cystatin C (urine)	Muller et al. (1999) [26]	71	Cystatin C > 1 mg/l	Specificity 84 % Sensitivity 84 %	
				Good correlation with serum creatinine at 1 year	
$\beta 2$ -micro-globulin (urine)	Muller et al. (1993) [25]	100	$\beta 2$ -microglobulin > 2 mg/l: poor	Specificity 83 % Sensitivity 80 %	
	Muller et al. (1999) [26]	71	$\beta 2$ -microglobulin > 5 mg/l: poor	Specificity 82 % Sensitivity 100 %	
				Good correlation with serum creatinine at 1 year	
	Anumba et al. (2005) [59]	113	$\beta 2$ -microglobulin > 13 mg/l: poor	Sensitivity 63 %	
	Craparo et al. (2007) [61]	12	$\beta 2$ -microglobulin > 13 mg/l: abnormal	Not predictive for potential response to shunting	

SD, Standard deviation

serum markers may be superior to urine analysis in predicting postnatal kidney function, it has to be kept in mind that individual outcomes are also dependent on other factors. More trials with larger prospective series and standardized thresholds are needed to predict the prognostic value of biochemical markers in fetal serum and urine [28].

It would appear that a combination of antenatal clinical (LUTO vs. ARPKD) and ultrasound data (degree of renal hypoplasia and ROH as well as time of diagnosis), ideally supplemented by MRI studies and evaluations of biochemical parameters may be a way to improve the predictive prognostic value. In a recent study by Spaggiari [29] the combination of

Table 2 Fetal serum markers of kidney function

Fetal marker	Reference	Number of patients	Assumed prognosis	Predictive value	Limitations
Cystatin C (serum)	Muller et al. (2004) [62]	54		Not significantly higher in cases with oligohydramnios	
	Bökenkamp et al. (2001) [63]	84	>2.06 mg/l increased	Specificity 91.8 % Sensitivity 63.6 % May be useful in prediction of postnatal renal function	
β 2-micro-globulin (serum)	Dommergues et al. (2000) [64]	77	β 2-microglobulin <5 mg/l: good β 2-microglobulin >5 mg/l: poor	Specificity 100 % Sensitivity 67 % Positive correlation between fetal β 2-microglobulin and postnatal creatinine	
	Bökenkamp et al. (2001) [63]	84	>5.6 mg/l increased	Specificity 85.5 % Sensitivity 90 % May be useful in prediction of postnatal renal function	False positive results due to infections, dependent on gestational age
	Muller et al. (2004) [62]	54	β 2-microglobulin <3.5 mg/l: good β 2-microglobulin >5 mg/l: poor	Significant correlation with postnatal serum creatinine when extrem values (<3.5 mg/l or >5 mg/l)	In hyper-echogenic kidney (i.e. in ARPKD) normal values are possible
	Craparo et al. (2007) [61]	12	β 2-microglobulin >4.9 mg/l: abnormal	Before shunting: not predictive for potential response to shunting After shunting: increase associated with poorer prognosis	
	Spaggiari et al. (2013) [29]	34	β 2-microglobulin >5 mg/l: poor	β 2-microglobulin predicts poor outcome	

ARPKD, Autosomal-recessive polycystic kidney disease

β 2-MG measurements and presence of ROH improved diagnostic accuracy, although patients with TOP were again included, thereby substantially limiting the conclusions.

Treatment options (ante- and postnatal)

Both antenatal and postnatal treatment issues of fetuses with severe bilateral renal disease with ROH are discussed in this section.

Antenatal treatment options for severe ROH include de-obstructive procedures in fetuses with LUTO and amnioinfusion to improve pulmonary maturation and outcome. Early reports, based on experimental models, detail surgical approaches to treating LUTO by the surgical placement of indwelling fetal shunt catheters [30]. A wide variety of interventions have been documented, including vesicoamniotic or renoamniotic shunting, single or multiple bladder or kidney aspirations, external kidney or bladder drainage and vesico- as well as ureterostomies. By 1987, 57 patients had already undergone such surgical interventions, including 28 patients (49 %) presenting with ROH. Complications were seen in 44 % of cases, and the overall survival was only 21 %. An improvement of renal function after surgical decompression in-utero was not seen in any patient with

LUTO and ROH [31]. In another series, 17 of 34 patients survived vesicoamniotic shunting beyond 2 years of age; 13 patients died in the postnatal period, six of whom had pulmonary hypoplasia [32]. Biard et al. [33] described a 1-year-survival of 91 % in a cohort of 18 fetuses who received vesicoamniotic shunting and found increased pulmonary survival as well as improved renal outcome. Nevertheless, 33 % were dependent on dialysis after birth, and 39 % retained pulmonary symptoms, mainly asthma [33]. In 2013 a prospective randomized controlled trial was performed, but due to poor recruitment only 31 patients with LUTO were included in this study [34, 35]. Survival was better—although not statistically—in fetuses with LUTO receiving vesicoamniotic shunting (8/16 vs. 4/15), and the overall long-term outcome was comparable; only two children survived for 2 years without renal impairment. Based on the results of this study, the authors concluded that vesicoamniotic shunting may improve perinatal survival but does not alter the poor long-term prospects of affected children. Therefore, the risk of the intervention has to be balanced against both the potential benefit for the patient and the costs [36]. The lack of impact of de-obstructive measures on kidney development may be explained by the fact that renal organogenesis is largely completed by the end of the second trimester.

It is debatable whether antepartum amnioinfusion can prevent or ameliorate the consequences or even the degree of pulmonary hypoplasia in neonates and fetuses. Experimental evidence is in favour of its use, which also seems to be supported by recent studies, at least in some cases after the premature rupture of membranes [37–39]. Systematic studies on fetuses with ROH have not been performed, yet a recent case report indicates a potential benefit even in a fetus with bilateral renal agenesis [40]. However, amnioinfusion is not without risk and may lead to abortion or rupture of membranes [41]. Thus, controlled studies or at least registries should be implemented—for example, to compare amnioinfusion to intrauterine surgery [42].

Postnatal treatment has changed dramatically in recent decades with the availability of modern neonatal intensive care and dialysis techniques; the latter allow blood purification even in neonates, improving the outcome of bilateral renal disorders with renal insufficiency. Clinical outcome data of published series addressing mortality as well as pulmonary and renal outcome are summarized in Table 3.

Series of short-term (and long-term) survival of patients with ROH often have methodological problems. In some series, fetuses after TOP are included, regarded as patients with “poor outcome” [29]. In other studies, survivors of ROH are not actively treated, thus increasing mortality. For example, Grijseels et al. [43] conducted a retrospective case series in which they analysed the outcome of 71 pregnancies complicated by ROH. They reported that of 25 liveborn neonates with different antenatal ultrasound findings, nine children (3 with dysplasia, 4 with polycystic kidneys and 2 with hydronephrosis) were not resuscitated because of the associated malformations, and treatment was withheld in an additional seven patients because of the suspected malformations. This study also included patients with very low birth weight, which might have had an impact on morbidity and mortality [43]. Studies which selectively examine fetuses with LUTO are limited by incomplete clinical data despite the probable inclusion of patients with ROH; for example, in a series of 15 patients with urethral valves, five of the patients died [44].

Mortality

Mehler et al. [45] published a mortality rate ranging from 30 to 36 % in a series of neonates with ROH who were treated by or referred to their institutions; this variability was reported to be due to neonatal mortality, especially pulmonary hypoplasia. In the period preceding 2012, we treated 50 patients of whom 13 died [26 %, unpublished observation; this rate includes patients who did not survive the neonatal period despite ventilation and also patients who died later due to other

complications, as may be expected from the underlying chronic kidney disease (CKD). In one report, survival until discharge was 64 % and pulmonary complications, as assessed by the bronchial oxygenation index, were the best predictor of mortality [45].

These data confirm that pulmonary hypoplasia is an important factor determining neonatal outcome in ROH. However, abnormal lung development may precede oligohydramnios, as shown in a transgenic murine model of renal dysgenesis [46], which might explain some of the clinical heterogeneity observed in children with severe ROH after birth. In detail, a knock-out mouse was generated with selective deletion of a protein that is important for the assembly of basement membranes. The mutation results in impairment of early kidney organogenesis and lung development [47]. Although development began during early embryogenesis in the homozygous knock-out mice lung, it was at all times significantly decreased compared to that of the wild type, thus suggesting a multifactorial causation of lung hypoplasia in the context of renal dysfunction. However, the pathogenesis of pulmonary hypoplasia remains incompletely understood. In a case report of monoamniotic twins discordant for bilateral renal agenesis with a single amnion cavity, no prenatal anomalies were described. However, one of the twins presented 24 h after birth without voiding and showing signs of renal failure. Bilateral renal agenesis was diagnosed and peritoneal dialysis (PD) started. The child never had respiratory difficulties, suggesting that ROH did not occur due to normal AFV in the healthy fetus [48]. On the other hand, in our series [49], one patient diagnosed with ROH at 19 weeks of gestation also did not have significant pulmonary problems postnatally, indicating that factors other than ROH may be relevant. Thus, more clinical and experimental studies of pulmonary hypoplasia in ROH are needed.

Some infants need only mild ventilator support, while others need ventilation for weeks. No study has yet reported a correlation between antenatal diagnosis of pulmonary hypoplasia and clinical outcome, even with the most sophisticated of technologies [50]. Even postnatal predictors of pulmonary complications, such as the best oxygenation index, are not completely specific, since treatment makes survival possible for some infants. It is of note that respiratory complications may be low, despite the presence of ROH. Some infants do not require ventilation at all or only for a short time. In our series, the median ventilation time was 4 (range 1–60) days [49], which underlines the unpredictability of the disease course. In the series by Mehler et al. [45], only 23/36 neonates required intubation. Overall in that series, 21 of the 36 neonates survived a median follow-up period of 96 months, of whom five had a normal renal function, four underwent kidney transplantation and 12 had persistent CKD. Whether infants surviving

Table 3 Outcome studies of fetuses with antenatal diagnosis of renal oligohydramnios

Reference	Study characteristics	Number of patients with ROH	IU deaths/TOP	Mortality [<i>n</i> (%)]	Pulmonary outcome	Neonatal renal failure	Long-term renal outcome
Ghor et al. [65]	56 patients with antenatal diagnosis of urinary tract disease	18	6	12/12 (100 %)	No data	No data	No data
Eckhold et al. [66]	24 boys with posterior urethral valves	4/24	0	0	Ventilation necessary in neonatal period (<i>n</i> =4)	No details	Renal transplantation at 4 and 5 years, respectively, in 2 children
Rani et al. [55]	18 patients with bladder outlet obstruction	14/18	0	12/14 patients with ROH	No data	No data	2/18
Bard et al. [33]	Male patients with lower urinary tract obstruction	20		2/20 (10 %)	2 deaths due to pulmonary hypoplasia; Half of patients suffers from long-term respiratory symptoms		Acceptable renal function (<i>n</i> =8) mild CKD (<i>n</i> =4) Dialysis & transplantation (<i>n</i> =6)
Zaccara et al. [67]	28 cases of bilateral obstructive uropathy during a 3-year period	18/28	4/18 patients with ROH (2 lost to followup)	3/12 (25 %) of the live born patients with ROH	3 neonatal deaths due to pulmonary hypoplasia	No data	CKD in survivors, mean serum creatinine 1.3 ± 0.2 mg/dl
El-Ghoneimi et al. [68]	40 boys with posterior urethral valves	6/40	0	0	No data	No data	1 CKD, 5 normal renal function
Klaassen et al. [49]	All patients with ROH referred for treatment after birth	23	0	7/23 (30 %); 4 deaths in neonatal period	14/23 requiring mechanical ventilation, 11/23 had pneumothorax	4/23 started PD in neonatal period, discontinuation possible in 2	Of 16 survivors, 8 required RRT, 8 could be managed conservatively
Mehler et al. [45]	36 neonates with ROH	36		13/36 (36 %); 7 within 2 days	Best oxygenation index <9.6	2/23 with neonatal RRT	
Grijseels et al. [43]	71 pregnancies with diagnosis of ROH	71	46	15/25 (60 %)	9 patients died without attempted resuscitation. 7 patients died with associated malformations: 2 deaths, Down syndrome with bronchopneumonia; 1 child with intracerebral bleeding	Of 10 survivors, 1 did not need ventilator support. 1 child with preemptive renal transplant, 2 on dialysis at age 2 and 5 years	Some neonates with very low birth weight. No patients without attempted resuscitation.
Hogan et al. [69]	34 patients with isolated CAKUT. In 19, TOP was proposed; in 10 of these cases, parents refused.	12	9 (not only patients with ROH)	5/12 in 1st month of life	No data		5 survivors with normal creatinine, 2 with ROH
Spaggiari et al. [29]	29/34 patients with severe bilateral hypoplasia	30/34 with ROH	21	2/13 survivors with ROH	No data		13 survivors, 2 died (1 with pulmonary hypoplasia, 1 with GFR of <10 ml/min/1.73 m ² at 1 month)

IU, Intrauterine; TOP, termination of pregnancy; ROH, renal oligohydramnios; CAKUT, congenital anomalies of the kidney and urinary tract; PD, peritoneal dialysis; RRT, renal replacement therapy; CKD, chronic kidney disease; GFR, glomerular filtration rate;

pulmonary complications after ROH have long-term problems has only been addressed incompletely, but an elevated risk of asthma has been documented [33].

Renal outcome

Older series documented a poor renal prognosis for fetuses with ROH [13, 51], leading the authors to conclude that these urological anomalies were incompatible with extra-uterine life. However, it has to be emphasized again that especially an abnormal renal cortical appearance (such as renal cortical cysts or renal parenchyma hyperechogeneity) as well as oligohydramnios are important indicators of a potentially poor postnatal renal function, although these parameters are difficult to quantify objectively. We believe that the statement of a general incompatibility of urological anomalies with extrauterine life is no longer valid. Some patients with ROH only have mild renal insufficiency after birth and do not require dialysis [49]. Those neonates with end-stage renal disease (ESRD) after birth can nowadays be treated by dialysis, mainly PD.

A recent report summarizing several registries reported a 2-year survival of 81 %, yet long-term problems associated with ESRD and chronic dialysis, such as growth retardation, anaemia and hypertension, remained challenging [52]. Also, the possibility of organ transplantation with complications due to immunosuppression needs to be taken into account. Thus, despite the advances which have been made, several dilemmas are present and need to be discussed with parents [53]. It should be noted, however, that some infants require dialysis only temporarily, as renal function may recover. The ethical dilemma of sustaining life versus prolonging dying through the initiation of dialysis has been elegantly summarized recently by Dionne and d'Agincourt-Canning [54]. These authors developed a multidisciplinary decision-making framework to reduce the moral distress in decision-making situations; within this framework, the counselling of families with ROH occupies a very special place since decision-making starts before birth. After delivery, the first decision is whether to resuscitate or not, and the start of dialysis often has to be made very early, when long-term prognosis is yet unclear. Clearly, further research is needed in this area.

Unfortunately, published series sometimes analyse neonatal mortality and intrauterine deaths, including TOP, together, so that an objective interpretation of overall clinical outcome is difficult. For example, both Rani et al. from Glasgow [55] and Gloor from the Mayo Clinic [56] reported a poor diagnosis. In the latter series, ROH was documented in 18 of 52 children with congenital anomalies of the kidney and urinary tract (CAKUT). All children died, with six intrauterine deaths among them. Rani et al. also

reported a high mortality in their series of 18 patients with isolated urethral obstruction of different etiology, with 12 deaths among them. A predictive model for renal impairment in prenatally diagnosed CAKUT has recently been developed. When prenatal bilateral hydronephrosis and ROH, as well as postnatal criteria (diagnosis and renal function) were taken into account, a probability of surviving without CKD stage III at the age of 10 years was estimated to be 98 % for the low-risk group and 58 % for the high-risk group [57]. However, predictive models for the fetus would be much more helpful in the form indicated above to allow antenatal risk assessment and improve counselling.

It should be emphasized that death and presence of severe CKD are not the only relevant outcome parameters. Other issues, such as neurological development, growth, hypertension and quality of life, are not sufficiently studied and need to be considered [58].

Practical issues in postnatal treatment

As with pulmonary management, postnatal planning and performance of dialysis needs to be addressed. In our experience, it is important to be prepared for complications and to discuss treatment options prior to delivery. This should be done both within the multidisciplinary team and with the parents after comprehensive genetic counselling. In our opinion, it is also important to discuss de-escalation strategies with families prior to birth.

The primary focus during the first days of life is clearly pulmonary management; delay of dialysis for at least 2 days is feasible in most instances.

Delivery in a tertiary centre with all sub-specialities on board, including availability of the latest respiratory techniques (e.g. high-frequency ventilation and nitric oxide), is mandatory. In our opinion the risk of complications (especially cerebral) related to prematurity should be avoided, whenever possible. All patients should receive steroids antenatally for lung maturation. In children with ARPKD and anuria, bilateral nephrectomy may be necessary to improve ventilation after birth (and prepare for PD). In our experience, unilateral nephrectomy is often not sufficient since contralateral kidney volume usually increases dramatically after this procedure. Bilateral nephrectomy may cause a substantial drop in blood pressure, which has to be anticipated and treated to avoid complications such as blindness. Pneumothorax may occur at any time even in non-ventilated patients and requires prompt treatment.

After pulmonary stabilization we discuss and start dialysis. Strict volume restriction is initially necessary and, if possible, the Tenckhoff catheter should be left unused for 1 day or so to allow healing and minimize leakage. We have used haemofiltration in neonates with

ROH where PD was unsuccessful, but this technique is clearly associated with higher risks.

Genetic counselling

Counselling families in those cases where fetal bilateral renal disease with ROH has been diagnosed is extremely difficult. The exact prediction of postnatal course (mild course vs. non-survival) is not possible. Additionally, there exist many centre- and national-specific practices in the management of ROH and also differences in the ethical considerations of TOP. Unfortunately, even nowadays family counselling is often performed by obstetricians alone, who often have no adequate knowledge of recent advances in the field of paediatric nephrology or neonatology. For this reason, the consequence is frequently a TOP. In some instances, counselling is performed by geneticists, especially for fetuses with ARPKD. In our opinion, parents are entitled to an extensive discussion of the potentially heterogeneous postnatal risks and outcome that reflects the advances in neonatology and paediatric nephrology. This is already the case of fetuses with cardiac malformations, for example, where the input of paediatric cardiologists is sought. It should be mentioned that disparity in termination rates between countries because of severe renal disease is important and is probably related to cultural, religious and legal issues. Moreover, the information given to the parents about dialysis initiated during the neonatal period is strongly dependent on local policy and experience.

On the other hand, CKD may occur in a significant proportion of patients, and parents have to be adequately informed about the long-term consequences of this. We have established an approach in our institution where obstetricians, neonatologists and paediatric nephrologists discuss the prognosis with the parents after ultrasound investigation. Ideally, back-up by a psychologist should be available as well.

Summary and conclusion

To summarize and conclude, the presence of ROH is a risk factor of perinatal mortality and postnatal renal outcome. Antenatal assessments of risk profiles predicting outcome have to be treated with caution as considerable clinical heterogeneity is present. This heterogeneity has to be taken into account when TOP is recommended, even though a decrease in the TOP rate may have implications for intrauterine deaths or postnatal complications, including mortality, if severely affected fetuses are allowed to survive. Therefore, counselling a family with an affected ROH-fetus is very challenging and requires a multidisciplinary approach, with specialist input supporting the affected parents' individual decision process (Fig. 1). If the decision is made to continue the pregnancy, every effort should be made to supply optimal postnatal care. To enhance future assessment of fetal outcome and morbidity, prospective registry data should be initiated addressing fetal complications and prognostic markers, as well as neonatal short- and long-term outcome and morbidity.

Fig. 1 Steps in the counselling of a family with a fetus with renal oligohydramnios

Conflict of interest The authors declare that they have no conflict of interest.

Multiple choice questions (answers are provided following the reference list)

- 1) The most frequent diagnoses leading to renal oligohydramnios are (please select two):
 - a. Cystinosis
 - b. Lower urinary tract obstruction with renal hypo/dysplasia
 - c. Autosomal recessive polycystic kidney disease
 - d. Primary hyperoxaluria type 1
 - e. Bilateral ureteric-pelvic junction obstruction
- 2) Renal oligohydramnios is associated with which two postnatal complications:
 - a. Prematurity
 - b. Pulmonary hypoplasia
 - c. Renal insufficiency
 - d. Intracerebral bleeding
 - e. Prolonged icterus neonatorum
- 3) Outcome of fetuses with renal oligohydramnios are (please select three answers):
 - a. Is easy to predict using clinical case series
 - b. Can be predicted using fetal urine and serum markers
 - c. Is difficult to predict because of clinical heterogeneity postnatally
 - d. Is dependent on initial patient care and therefore referral to experienced centers is important
 - e. Is usually determined by presence of initial pulmonary morbidity
- 4) The following pulmonary complications after renal oligohydramnios have to be anticipated (please select two answers):
 - a. Pneumothorax
 - b. Pulmonary hypoplasia with need of mechanical ventilation
 - c. History of allergic asthma in childhood
 - d. Risk of recurrent pneumonia
 - e. The risk of pulmonary problems is low and can be neglected
- 5) Counselling of families in the presence of renal oligohydramnios (please select three answers):
 - a. Is not necessary since outcome is always fatal. Termination of pregnancy should be performed as early as possible.

- b. Is difficult due to the potentially heterogeneous clinical course after delivery.
- c. Should be performed by obstetricians alone or a geneticist in the situation of ARPKD.
- d. Should be performed by a multidisciplinary team including obstetricians, neonatologists, paediatric nephrologist and ideally a psychologist.
- e. Should include adequate information about long-term medical consequences (e.g. chronic renal disease, dialysis and chronic morbidity)

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Answers

- 1: b, c
- 2: b, c
- 3: c, d, e
- 4: a, b
- 5: b, d, e